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Intrapleural minocycline following simple aspiration for initial treatment of primary spontaneous pneumothorax

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KEYWORDS
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Summary
Background: The optimal initial management of primary spontaneous pneumothorax (PSP) remains controversial. This study was to evaluate the safety and efficacy of intrapleural minocycline following aspiration for initial treatment of PSP.
Methods: Between January 2004 and November 2006, 64 patients with a first episode of PSP were successfully treated by simple aspiration using pigtail or intravenous needle catheter. From December 2005, 31 of the patients also received 300 mg of minocycline hydrochloride post lung expansion, instilled through the catheter into the pleural space (minocycline group). The control group consisted of the first 33 patients of the series who had successfully undergone simple aspiration alone between January 2004 and December 2005.
Results: There was no significant difference between the two groups in terms of demographic data. Patients in the minocycline group had higher doses of meperidine injection. The group hospitalization rates and mean hospital stays were comparable. After a mean follow-up of 13 months (range 3–26), recurrence was noted in 4 of the minocycline group and 11 of the control group (12.9% versus 33.3%, $p = 0.045$). Subsequent thoracoscopic surgery for the recurrent patients revealed that minocycline induced scant loose adhesions which did not significantly affect operation procedures. The long-term pulmonary function and rates of residual pain for the two groups were comparable.

Abbreviation: PSP, primary spontaneous pneumothorax.

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Conclusions: Although associated with immediate chest pain, intrapleural minocycline following simple aspiration is a simple, safe and convenient initial treatment for PSP that may reduce the rates of ipsilateral recurrence.

Introduction

Primary spontaneous pneumothorax (PSP) most commonly occurs in young, tall, lean males.[1,2] The estimated recurrence rate is 23–50% after the first episode.[3–5] This high recurrence rate has stimulated development of many different therapeutic approaches, ranging from conservative treatment, such as observation, to more invasive therapies, including surgery.[6] Optimal treatment for patients presenting with a first episode of PSP remains controversial. In the recently published British Thoracic Society (BTS) guidelines, simple aspiration is recommended as the first-line treatment for all PSP cases requiring intervention because this treatment provides the advantage of reduced hospital admission rate and decreased hospital stay when compared with chest tube drainage.[4] However, the recurrence rate with this procedure is around 30%, making it inappropriate as a standard of care.[7,8]

Intrapleural instillation of a chemical irritant (chemical pleurodesis) is an effective way to reduce the rates of recurrent spontaneous pneumothorax in surgical and non-surgical patients.[9–11] Previously, chemical pleurodesis has typically been administered through chest tube or thoracoscopy.[9–13] Administration of sclerosing agents through intravenous needle or pigtail catheter after simple aspiration has not previously been reported and, therefore, the safety and efficacy of this simple procedure remain unknown.

As our recurrence rate after simple aspiration had continued to remain high, we began to instill minocycline into the pleural cavity through the pigtail or intravenous needle catheter from December 2005 to determine if this adjuvant was effective in terms of reducing the recurrence rate. In the present study, we report our experience of minocycline pleurodesis for treatment of a first episode of PSP after successful aspiration of pneumothorax. The effects of this adjuvant therapy were evaluated by comparing the outcomes for patients who underwent the simple aspiration with or without additional minocycline pleurodesis.

Patients and methods

Study design

The aims of this retrospective study were to evaluate the safety and efficacy of additional minocycline pleurodesis after simple aspiration for preventing recurrence of a first episode of PSP. From January 2004 to December 2005, nothing was administered to the pleural cavity after successful aspiration of PSP (control group). Since December 2005, we began to instill minocycline through the aspiration catheter to attempt to decrease the incidence of ipsilateral recurrence of pneumothorax.

Patient selection and institutional review board approval

From January 2004 to November 2006, all patients with the diagnosis of spontaneous pneumothorax admitted to the emergency department (ED) or general wards of a 2600-bed university teaching hospital with an ED annual census of around 100,000 patient-visits were identified. After careful review of the medical records, only patients who underwent manual aspiration as their initial treatment were selected. To avoid cases of recurrent or secondary spontaneous pneumothorax, patients with a previous history of spontaneous pneumothorax, aged over 50 years, or with preexisting pulmonary diseases were excluded. Unsuccessful aspiration requiring further chest tube insertion and thoracoscopic surgery were additional exclusion criteria. The selection criteria for patients with or without minocycline pleurodesis were the same. This study was approved by the Institutional Review Board of National Taiwan University Hospital.

Manual aspiration and minocycline pleurodesis

Informed consent was obtained from all subjects before the procedure. Manual aspiration was performed as follows: patients were seated in semi-supine position. After skin disinfection and field preparation, a small-caliber Teflon intravenous needle (Surflo, 16 or 18 Ga; Terumo Corporation, Tokyo, Japan) or pigtail catheter (six or eight French; Bioteque Corporation, I-Lan, Taiwan) was introduced into the second or third intercostal space, at the midclavicular line, after local anesthesia with 2% lidocaine. After the catheter had entered the pleural space, it was fixed to the skin using sterile adhesive tape and connected via a three-way valve to a 50-ml syringe. Air was manually aspirated, until a resistance was felt and aspiration ceased. Thereafter, chest radiography (CXR) was performed with the catheter in place. If the CXR confirmed that there was no pneumothorax or only a very small one with improvement of symptoms, then the patient was admitted to the ER observation unit or the general ward for observation or minocycline pleurodesis. Pneumothoraces that failed to resolve after aspiration were treated by chest tube drainage or thoracoscopic surgery, at the discretion of the attending physicians.

Pleurodesis patients received 30 ml of 1% lidocaine hydrochloride (300 mg) followed by a solution of 30 ml of normal saline containing 300 mg of minocycline (Mirosin®; Taiwan Panbiotic Laboratories, Kaohsiung, Taiwan) instilled into the pleural cavity through the intravenous needle or pigtail catheter. Patients were repositioned every 30 min so

that the minocycline could contact all pleural surfaces.[10,11] Side effects and complaints were recorded. CXR at 4–6 h after aspiration with/without minocycline administration was evaluated, with the catheter removed when complete expansion of the lung or only a very small rim of apical air detected in all cases.

Estimation of pneumothorax size

The CXR was carefully reviewed in each case and the pneumothorax size estimated using Light's formula (estimated pneumothorax percentage $= (1-L3/H3) \times 100$; where $H =$ mean hemothorax diameter and $L =$ mean diameter of lung "collapse").[14]

Pulmonary function analysis

Pulmonary function tests were performed for non-recurrent patients able to attend a hospital outpatient appointment at least 6 months after aspiration. Forced vital capacity (FVC) and forced expiratory volume in 1 s ($FEV_{1.0}$) were measured using a spirometer (Microspiro HI-298; Chest Corporation, Tokyo, Japan) in the seated position. A minimum of three acceptable forced expiratory maneuvers were performed, with the best selected for analysis.

Data collection and analysis

The data, including patient demographics, radiographic size of pneumothorax, volume of air aspirated, hospitalization rates, duration of observation, complications, and operative findings and results, were collected through retrospective chart review and documentation of database information. Follow-up was in the form of clinical visits or telephone conversation; interval range was 3–26 months (mean 13). Residual pain was evaluated for non-recurrent patients at least 6 months after aspiration on a 0–5 pain scale, with the integers representing freedom from pain, occasional discomfort, occasional analgesia, non-opiate analgesia, opiates for regular pain, and severe and intractable pain, respectively.[15] Continuous variables, such as age and weight, are expressed as mean $\pm$ standard deviation, with the two-sample t-test used for analysis. Categorical variables, including gender and smoking status, are presented as frequency (%) and analyzed by Fisher's exact test. Scores for residual chest pain were analyzed using the Wilcoxon rank-sum test. The Kaplan–Meier method was used to evaluate freedom from recurrence, and the log-rank test was applied for comparisons. A p-value of less than 0.05 was considered significant for all tests.

Results

Between 2004 and 2006, a total of 93 patients with spontaneous pneumothorax were managed by simple aspiration using pigtail ($n = 69$) or intravenous needle catheter ($n = 24$) at our ED. Of these, 29 individuals were excluded from the study because of: age (>50 years; $n = 2$); preexisting pulmonary disease ($n = 1$); unsuccessful aspiration ($n = 24$); or, loss to follow-up after treatment ($n = 2$). Of the remaining 64 subjects, 34 underwent simple aspiration alone while 31 underwent additional minocycline pleurodesis before catheter removal. There were no significant between-group differences comparing demographic data, pneumothorax size, or aspirated volume (Table 1). The treatment results are summarized in Table 2. No procedure-related complications were observed in either group. Chest pain was a common complaint after minocycline instillation, with severe pain that required immediate meperidine injection occurring in 12 patients (38.7%) in the minocycline group but only 2 (6.1%) of the controls ($p = 0.002$). The mean accumulated dose of meperidine was also higher for the minocycline group (48.3 mg versus 16.7 mg; $p = 0.029$). Five minocycline patients were admitted for 1–3 days for wound pain ($n = 1$), incomplete absorption of pneumothorax ($n = 1$), or observation only ($n = 3$). Four of the controls were admitted for 1–4 days for incomplete absorption of pneumothorax ($n = 1$) or observation only ($n = 3$). Group hospitalization rates and mean duration of observation are comparable.

After a mean follow-up of 13 months (range 3–26), recurrent ipsilateral pneumothorax was noted in four minocycline patients (12.9%) and 11 controls (33.3%) ($p = 0.045$, Kaplan–Meier method and log-rank test). The rates of freedom from recurrence (Kaplan–Meier method) for both groups are plotted in Figure 1. The divergence of the two curves almost immediately after aspiration indicates that patients in the minocycline group had a lower rate of recurrence and greater latency. Twelve out of 14 recurrent patients (minocycline group: 3, observation

Table 1 Clinical characteristics of patients with and without additional minocycline pleurodesis after aspiration.

	Minocycline group ($N = 31$)	Observation group ($N = 33$)	p-Value
Age (year)*	22.7 $\pm$ 8.1	23.7 $\pm$ 8.1	0.616
Sex (male)	28 (90.3%)	25 (75.8%)	0.186
BMI*,†	19.1 $\pm$ 1.2	19.2 $\pm$ 2.2	0.940
Smoking	15 (48.4%)	10 (30.3%)	0.200
Side involved (left)	17 (54.8%)	20 (60.6%)	0.801
Pneumothorax size (%)*,‡	53.7 $\pm$ 16.1	54.8 $\pm$ 14.0	0.763
Aspirated volume (ml)*	867.1 $\pm$ 395.6	909.1 $\pm$ 578.0	0.737

*Mean $\pm$ S.D.
†BMI, body mass index.
‡Estimated by Light's formula.

Table 2 Treatment results for patients with and without additional minocycline pleurodesis.

	Minocycline group ($N = 31$)	Observation group ($N = 33$)	p-Value
Meperidine requested	12 (38.7%)	2 (6.1%)	0.002
Dose of meperidine (mg)*	48.3±5.8	16.7±25.8	0.029
Complication	0 (0%)	0 (0%)	1.000
Hospitalization	5 (16.1%)	4 (12.1%)	0.729
Duration of observation (h)*	23.2±17.6	24.2±18.9	0.830
Recurrence	4 (12.9%)	11 (33.3%)	0.077
Pulmonary function test*,†			
FVC‡	98.2±12.0	98.7±11.1	0.904
$FEV_{1.0}$‡	98.5±12.2	103.0±9.5	0.246
Residual pain§			
Pain free	18 (69.2%)	15 (83.3%)	0.294
Occasional discomfort	8 (30.8%)	3 (16.7%)	
Occasional use of analgesics	0 (0%)	0 (0%)	

FVC, force vital capacity; $FEV_{1.0}$, force expiratory volume in 1 s.

*Mean±S.D.

†Twenty patients in the minocycline group and 15 in observation group were available for spirometric measurement.

‡FVC and $FEV_{1.0}$ are presented as percentage of predictive value.

§Twenty-six patients in the minocycline group and 18 in the observation group were available for residual pain evaluation, and analyzed by Wilcoxon rank-sum test.

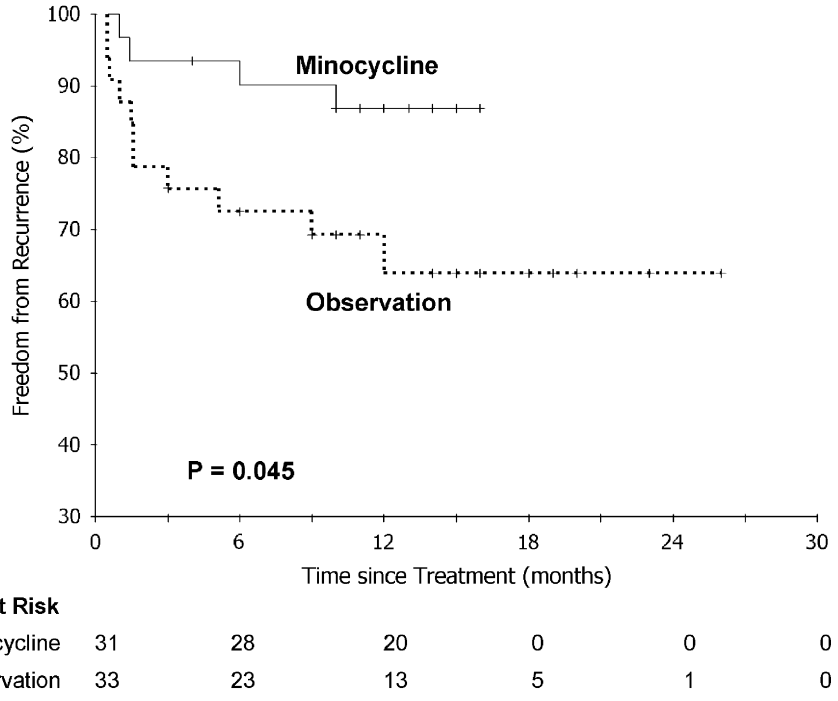

Figure 1 Freedom from recurrent pneumothorax in patients with or without additional minocycline pleurodesis after simple aspiration. The number of patients at risk for each 6-month period is indicated under the corresponding time point.

group: 9) subsequently underwent thoracoscopic bullectomy and mechanical pleurodesis, with no complications occurring. The surgical findings and results for both groups were comparable in terms of blood loss, surgical duration, and postoperative stay (Table 3). On thoracoscopy, two minocycline patients (66.7%) had pleural adhesions, while no adhesions were noted in the controls ($p = 0.045$). The adhesions were scant and loose, and mainly located in the anterior superior pleural cavity where the minocycline was instilled (Figure 2). The adhesions were easily freed using endoscopic instruments and did not significantly affect thoracoscopic procedures and outcomes.

To evaluate the long-term effects of minocycline pleurodesis in terms of pulmonary function and chest pain, 35

Table 3 Operation findings and results for recurrent patients with or without additional minocycline pleurodesis.

	Minocycline group ($N = 3$)	Observation group ($N = 9$)	p-Value
Age (year)*	25.0±8.1	22.8±8.1	0.755
Sex (male)	3 (100%)	7 (77.8%)	>0.99
Smoking	2 (66.7%)	2 (22.2%)	0.236
Pleural adhesions	2 (66.7%)	0 (0%)	0.045
Blood loss (ml)*	76.7±25.5	66.7±31.2	0.629
Duration of operation (min)*	88.3±33.3	78.9±34.6	0.643
Postoperative stay (day)*	4.0±1.0	3.8±1.1	0.763

*Mean±S.D.

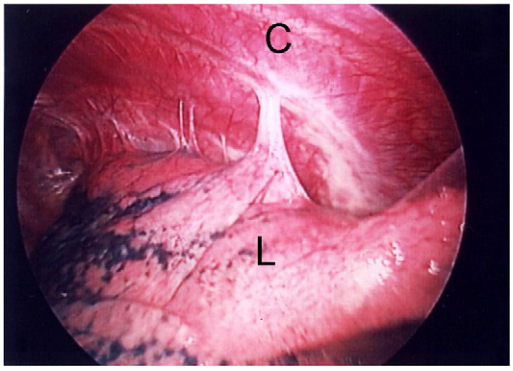

Figure 2 Pleural adhesions in a recurrent patient after minocycline instillation. C: chest wall; L: lung.

patients were available for spirometric measurement and 44 for residual pain evaluation (20/15 and 26/18 in the minocycline/observation groups, respectively). The results show that the two groups had comparable FVC and $FEV_{1.0}$. Most patients were pain free. Only 11 individuals experienced occasional discomfort during the follow-up period, however, analgesics were not required. Group scores for residual chest pain were also comparable (Table 2).

Discussion

This study demonstrates that minocycline pleurodesis following simple aspiration provides a safe, easy, noninvasive, and convenient initial treatment for PSP that may reduce the rates of recurrence.

The initial management of PSP has been a subject of controversy. Choice of initial treatment includes observation,[4] simple aspiration,[5,8,16–18] chest tube drainage,[4,5,7] chest tube drainage with sclerosis,[9,13] medical thoracoscopy,[12] and video-assisted thoracoscopic surgery (VATS).[19] Among the published methods, prevention of recurrence can only be obtained by chest tube drainage with sclerosis, medical thoracoscopy, or VATS. However, VATS is not suggested as the initial treatment for PSP by most physicians because it results in 70% of patients undergoing unnecessary operations. Talcage via medical thoracoscopy for PSP is more cost-effective than chest tube drainage[12]; however, admission is required and the procedure must be performed by a specialist. Because of the invasiveness and inconvenience of the available methods, there is quite good consensus that procedures to prevent recurrence should be reserved for the second pneumothorax.[4–6]

In their prospective randomized trial, Light et al. showed that intrapleural tetracycline instillation is effective for diminishing the rate of recurrence for patients with spontaneous pneumothorax who are hospitalized and treated with tube thoracostomy.[9] Further, tetracycline pleurodesis decreased the recurrence rate from 31.8% to 10.5% and from 43.0% to 28.2% in patients with PSP and secondary spontaneous pneumothoraces, respectively. Another randomized study comparing the pneumothorax recurrence after chest tube drainage without and with tetracycline found recurrence rates of 36% and 13%, respectively.[13] Our recurrence rates for simple aspiration alone or with minocycline pleurodesis (33.3% and 12.9%) are similar to those of the above two studies, indicating that tetracycline-based pleurodesis remains effective regardless of whether administration is via chest tube or aspiration catheter.

The most commonly used methods for air evacuation are simple aspiration and chest tube drainage. These is now compelling evidence that simple aspiration should be considered the primary treatment in uncomplicated PSP because it appears to be as effective as chest tube drainage.[7,8,17,18] Further, compared to the latter, the advantages of reduced hospital admission rate and decreased stay associated with simple aspiration translate into economic benefits.[16,21] Furthermore, placement of an aspiration catheter is easier than a chest tube, with the complication rate also lower.[4,22] In addition to demonstrating the safety of simple aspiration in PSP, our data also show that minocycline can be easily administered through the aspiration catheter without increasing the complication rate and hospital stay.

Although chemical pleurodesis is effective in terms of reducing the rate of recurrence, the recently published guidelines do not recommend it as the initial treatment for PSP because pleural adhesions may interfere with subsequent surgery in the event of recurrence, and operation remains the standard of care in recurrent patients.[4,5] In our cohort, three recurrent patients in the minocycline group underwent thoracoscopic bullectomy and apical pleurectomy. Although scant, loose adhesions were noted intrasurgically in two of these cases, these did not affect the

thoracoscopic procedure. Further, mean operation time, blood loss and postoperative stay were comparable to analogous control patients who did not undergo minocycline pleurodesis. A possible explanation for this finding is that minocycline induces variety degrees of pleural adhesions, with recurrence only occurring in patients with loose or no adhesions.

In this study, minocycline was selected for the chemical pleurodesis because this tetracycline derivative is comparably safe, inexpensive and widely available. Minocycline also compares favorably with tetracycline in terms of demonstrated efficacy of pleurodesis in a lapin model.[20] Most importantly, minocycline hydrochloride is easily administered through aspiration catheters of very small caliber. In contrast, talc is not suitable for delivery via pigtail or intravenous needle catheter. Although talc may have a lower recurrence rate, it must be applied surgically or thoracoscopically, and admission is required.[12]

Another concern with minocycline pleurodesis is the risk of constrictive pulmonary dysfunction after minocycline instillation. Our study showed that the long-term FVC and $FEV_{1.0}$ data for the two treatment groups were comparable, suggesting minocycline pleurodesis does not cause significant impairment of pulmonary function after simple aspiration.

Chest pain was the most common complaint associated with minocycline pleurodesis.[10,11] Although an intrapleural dose of 300 mg of lidocaine had been administered before minocycline instillation, our results show that meperidine was immediately required in 39% of the patients. Additionally, the mean meperidine dose was significantly higher in the minocycline group. However, the group scores for long-term residual chest pain were low and similar, suggesting that minocycline pleurodesis was not associated with higher incidence of residual chest pain. In general, minocycline instillation proved safe in our sample, with no pleural effusions or infections noted.

We accept that this was a retrospective investigation, with comparison based on a historical control; nevertheless, our results show that minocycline pleurodesis can be easily and safely applied after successful simple aspiration for PSP without increasing hospital stay or complication rates. In addition, minocycline pleurodesis does not appear to affect subsequent treatment when surgical intervention is required. As our results also suggest that minocycline following simple aspiration may decrease the rates of pneumothorax recurrence, further prospective randomized trials are needed to rigorously test the efficacy of this method as the initial treatment for PSP.

Conflict of interest statement

All authors have no personal relationships, and no commercial associations or sources of support that might pose conflicts of interest.

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References

1. Gobbel Jr WG, Rhea WG, Nelson IA, Daniel Jr RA. Spontaneous pneumothorax. *J Thorac Cardiovasc Surg* 1963;**46**:331–45.
2. Lichter J, Gwynne JF. Spontaneous pneumothorax in young subjects. *Thorax* 1971;**25**:409–17.
3. Light RW. Management of spontaneous pneumothorax. *Am Rev Respir Dis* 1993;**148**:245–58.
4. Henry M, Arnold T, Harvey J, Pleural Diseases Group, Standards of Care Committee, British Thoracic Society. BTS guidelines for the management of spontaneous pneumothorax. *Thorax* 2003;**58**(Suppl. 2):39–52.
5. Baumann MH, Strange C, Heffner JE, et al. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. *Chest* 2001;**119**:590–602.
6. Tschopp JM, Rami-Porta R, Noppen M, Astoul P. Management of spontaneous pneumothorax: state of the art. *Eur Respir J* 2006;**28**:637–50.
7. Noppen M, Alexander P, Driesen P, Slabbynck H, Verstraeten A. Manual aspiration versus chest tube drainage in first episodes of primary spontaneous pneumothorax: a multicenter, prospective, randomized pilot study. *Am J Respir Crit Care Med* 2002;**165**:1240–4.
8. Ayed AK, Chandrasekaran C, Sukumar M. Aspiration versus tube drainage in primary spontaneous pneumothorax: a randomized study. *Eur Respir J* 2006;**27**:477–82.
9. Light RW, O'Hara VS, Moritz TE, et al. Intrapleural tetracycline for the prevention of recurrent spontaneous pneumothorax. *JAMA* 1990;**264**:2224–30.
10. Chen JS, Hsu HH, Kuo SW, et al. Effects of additional minocycline pleurodesis after thoracoscopic procedures for primary spontaneous pneumothorax. *Chest* 2004;**125**:50–5.
11. Chen JS, Hsu HH, Chen RJ, et al. Additional minocycline pleurodesis after thoracoscopic surgery for primary spontaneous pneumothorax. *Am J Respir Crit Care Med* 2006;**173**:548–54.
12. Tschopp JM, Boutin C, Astoul P, et al. Talcage by medical thoracoscopy for primary spontaneous pneumothorax is more cost-effective than drainage: a randomized study. *Eur Respir J* 2002;**20**:1003–9.
13. Almind M, Lange P, Viskum K. Spontaneous pneumothorax: comparison of simple drainage, talc pleurodesis, and tetracycline pleurodesis. *Thorax* 1989;**44**:627–30.
14. Noppen M, Alexander P, Driesen P, Slabbynck H, Verstraete A, Vlaamse Werkgroep voor Medische Thoracoscopie en Interventionele Bronchoscopie. Quantification of the size of primary spontaneous pneumothorax: accuracy of the Light index. *Respiration* 2001;**68**:396–9.
15. Chen JS, Hsu HH, Kuo SW, et al. Needlescopic versus conventional video-assisted thoracoscopic surgery for primary spontaneous pneumothorax: a comparative study. *Ann Thorac Surg* 2003;**75**:1080–5.
16. Harvey J, Prescott RJ. Simple aspiration versus intercostal tube drainage for spontaneous pneumothorax in patients with normal lungs. British Thoracic Society Research Committee. *BMJ* 1994;**309**:1338–9.
17. British Thoracic Society Research Committee. Comparison of simple aspiration with intercostal drainage in the management of spontaneous pneumothorax. *Thorax* 1993;**48**:430–1.
18. Andrivet P, Djedaini K, Teboul JL, Brochard L, Dreyfuss D. Spontaneous pneumothorax. Comparison of thoracic drainage vs immediate or delayed needle aspiration. *Chest* 1995;**108**:335–9.
19. Margolis M, Gharagozloo F, Tempesta B, Trachiotis GD, Katz NM, Alexander EP. Video-assisted thoracic surgical treatment of

initial spontaneous pneumothorax in young patients. *Ann Thorac Surg* 2003;**76**:1661–3.
20. Light RW, Wang NS, Sassoon CSH, Gruer SE, Vargas FS. Comparison of the effectiveness of tetracycline and minocycline as pleural sclerosing agents in rabbits. *Chest* 1994;**106**: 577–82.
21. Packham S, Jaiswal P. Spontaneous pneumothorax: use of aspiration and outcomes of management by respiratory and general physicians. *Postgrad Med J* 2003;**79**:345–7.
22. Chan L, Reilly KM, Henderson C, Kahn F, Salluzzo RF. Complication rates of tube thoracostomy. *Am J Emerg Med* 1997;**15**: 368–70.